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Endothelium-Dependent Pulmonary Artery Responses in Chronic Heart Failure: Influence of Pulmonary Hypertension

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Objectives. **The purpose of this study was to determine whether pulmonary artery responses to acetylcholine are abnormal in patients with chronic heart failure.**

Background. **Defective pulmonary artery endothelium-dependent responses have been observed in chronic heart failure models in animals. However, pulmonary artery endothelial responses in humans with chronic heart failure are unknown.**

Methods. **Twenty-two patients with chronic treated heart failure (12 with secondary pulmonary hypertension, Group I; 10 with normal pulmonary artery pressure, Group II) and 8 control patients constituted the study groups. Intravascular ultrasound measurements of pulmonary artery area just beyond the tip of an 8F infusion sheath were obtained in response to acetylcholine (10^{-6}, 10^{-5} and 10^{-4} mol/liter). The 10^{-6} mol/liter infusion was repeated after methylene blue infusion. Indomethacin (5 μg/ml) was sequentially added to this combination in 17 patients.**

Results. **There were no significant differences among the three groups in vascular area responses to the lowest concentration (10^{-6} and 10^{-5} mol/liter) of acetylcholine, but the 10^{-4} mol/liter infusion resulted in significant constriction in Group II patients ($p < 0.05$, analysis of variance [ANOVA]). Pretreatment with methylene blue in Group II also resulted in significant pulmonary artery vasoconstriction to even the 10^{-6} mol/liter acetylcholine infusion (10.4 ± 7.8% in Group II vs. 1.7 ± 3.9% in the control group and 0.1 ± 4.3% in Group I, $p < 0.05$, ANOVA). The addition of indomethacin resulted in reversal of the constriction in Group II patients.**

Conclusions. **These responses indicate that the pulmonary artery endothelium may play a significant role in inhibiting vasoconstriction in patients with chronic heart failure who maintain normal pulmonary artery pressure.**

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Chronic left-sided congestive heart failure has been shown pathologically to result in significant intimal hyperplasia of the pulmonary vasculature (1). In many of these patients, significant pulmonary hypertension also develops, whereas others with a similar degree of left ventricular failure maintain normal pulmonary artery pressure. The mechanism for maintaining normal pulmonary artery pressure in this setting is unknown. Recent investigations in chronic heart failure models in animals (2) have shown that pulmonary artery endothelium-dependent responses may be defective. The most dramatic consequence of this defective response in the animal model was enhanced constrictor responses in the pulmonary circulation. It is unknown, however, whether humans with chronic heart failure develop abnormal pulmonary artery endothelial responses.

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High frequency intravascular ultrasound has been validated as a method of quantifying pulmonary artery area in vivo in humans (3). Vessel area obtained with this technique correlates closely with that obtained using digital angiography (4). Therefore, we used this imaging modality to study pulmonary artery endothelial responses in humans with chronic heart failure.

Methods

Study patients. Twenty-two patients (12 with chronic treated congestive heart failure secondary to left ventricular systolic dysfunction and mean pulmonary artery pressure >25 mm Hg [Group I] and 10 with clinically similar chronic treated heart failure and normal pulmonary artery pressures [Group II]) constituted the study group. The median New York Heart Association functional class at the time of study for both Groups I and II was class III. There was no significant difference between Groups I and II in the use of angiotensin-converting enzyme inhibitors (9 in Groups I and II), digoxin (8 in Group I, 5 in Group II) or diuretic agents (12 in Group I, 8 in Group II). Four patients in Group I and two in Group II were receiving calcium channel blocking agents at the time of study.

Eight age-matched control patients with coronary artery

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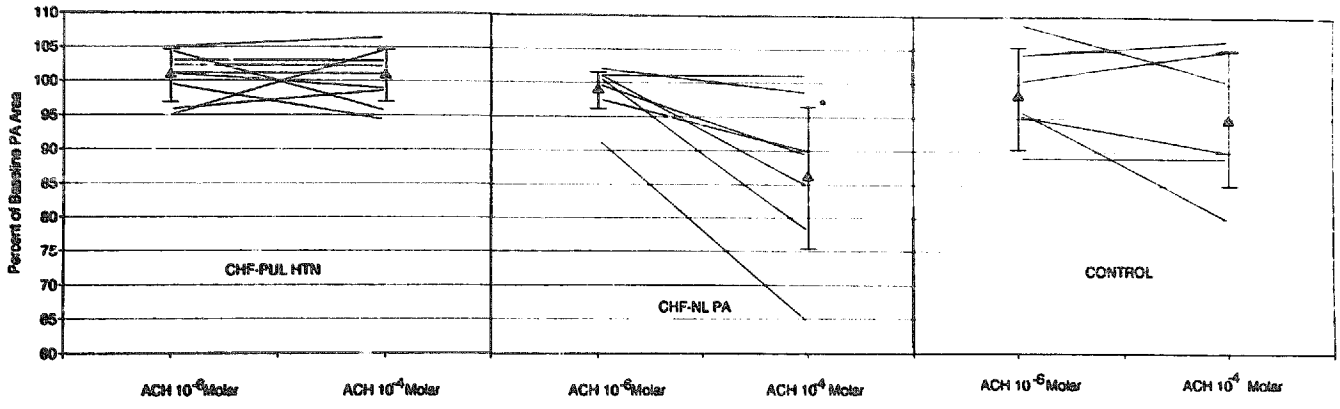

Figure 1. Graphic demonstration of the mean and individual changes in pulmonary artery (PA) area in response to 10^{-6}, 10^{-5} and 10^{-4} mol/liter of acetylcholine (ACH). There was significant vasoconstriction in the heart failure group with normal pulmonary artery pressure (CHF-NL PA) in response to the 10^{-4} mol/liter dose of acetylcholine. CHF-PUL HTN = heart failure group with secondary pulmonary hypertension. *$p < 0.05$ (analysis of variance).

disease, normal left ventricular systolic function by single-plane left ventriculography (mean left ventricular ejection fraction 59 ± 5%) and normal pulmonary artery pressures at right heart catheterization constituted the control group. Six control patients had two-vessel coronary artery disease; one had three-vessel disease and one had no significant coronary artery disease. Medications used by the control patients included angiotensin-converting enzyme inhibitors for hypertension (five patients), calcium channel blockers (two patients) and aspirin (three patients). All nitroglycerin-containing medications were discontinued for a minimum of 18 h before intravascular study. The study was approved by the Committee on the Conduct of Human Research at Virginia Commonwealth University and the Research Committee of the McGuire Veterans Affairs Medical Center.

Instrumentation. Studies were performed with the patient resting in the supine position and premedicated with 1 to 6 mg of midazolam. Intravascular ultrasound and Swan-Ganz pressure catheters were placed from the right femoral vein. A 5F or 8F arterial sheath was placed in the right femoral artery for continuous arterial pressure monitoring. A 7F Swan-Ganz catheter was advanced into the pulmonary artery to obtain mean and phasic pulmonary artery and capillary wedge pressures as well as thermodilution cardiac output. Arterial and mixed venous oxygen saturation were obtained during the experimental protocol in 21 patients.

Intravascular ultrasound imaging was accomplished using a commercially available ultrasound probe (Sonicath, Boston Scientific Corporation). This device is a 6F disposable catheter that encloses a 20-MHz ultrasound crystal at its tip and has an optimal axial resolution of 0.3 mm and optimal lateral resolution of 0.5 mm. The catheters were advanced into the pulmonary artery just beyond the tip of a 7F or 8F long infusion sheath (Cordis Corporation) using fluoroscopic guidance. The sheath was then used to deliver incremental concentrations of acetylcholine according to the methods outlined in Experimental Protocol. Baseline flow in the vessel studied was calculated by determining the pulmonary vascular area obtained with intravascular ultrasound and multiplying it by the mean velocity obtained with an end-mounted Millar Doppler crystal (3.5F) (DC-101, Millar Instruments). The Doppler crystal was advanced into the same pulmonary arterial segment as the ultrasound catheter, through the sheath immediately before placing the ultrasound probe. The product of the intravascular ultrasound-planimetered area and velocity (in cm^3/s) was used to determine the molar concentrations of acetylcholine to be infused, as follows:

$$Q_b(\text{ml/min}) \cdot M_{Ach} \cdot 182\text{g Ach/mol per liter} \cdot 1\text{ min/ml} =$$

grams of acetylcholine to place in 1,000 ml of normal saline solution at 1ml/min,

where 1.0 ml/min was the infusion rate for all study drugs; Q_b = baseline pulmonary artery flow from Doppler and area measurements; and M_{Ach} = molar concentration of acetylcholine desired (mol/liter). The same calculation was used for the methylene blue infusion (374 g/mol per liter). The same vascular region for the entire study was verified by periodic fluoroscopy (Fig. 1) and by specific vascular ultrasound markers (small vascular branches [≤1 mm], vascular geometry, bright echogenic structures in a specific region of the vascular wall) that confirmed a stable position of the catheter. Pulmonary artery plaque in the region being analyzed was defined as regions of different echo intensity that appeared to be attached to or part of the intima and that disrupted the homogeneous echo intensity of the vessel wall (5).

Experimental protocol. Incremental doses of acetylcholine (10^{-6}, 10^{-5} and 10^{-4} mol/liter) were infused in the pulmonary artery segment for 15-min intervals through the

Table 1. Baseline Clinical Characteristics of the Three Patient Groups

	Group I (n = 12)	Group II (n = 10)	Control Group (n = 8)
Age (yr)	55 ± 11	56 ± 10	62 ± 5
Heart failure duration (mo)	43 ± 28	42 ± 14	—
Etiology of cardiomyopathy			
Ischemic	7	7	—
Other	5	3	—
Chest roentgenogram			
Pulmonary edema	7/12	0/12	—
Pleural effusion	1/12	2/12	—
Cardiomegaly	12/12	8/10	
Pulmonary function tests			
FEV1 (%)	81 ± 10	81 ± 10	—
TLC (liters)	6.5 ± 1.5	6.1 ± 1.2	—
LVEF (%)	20 ± 6	21 ± 6	59 ± 5
PCW (mm Hg)	25 ± 7	10 ± 4	6 ± 2
Cardiac output (liters/min)	4.7 ± 1.6	4.6 ± 1.1	4.7 ± 0.6
Pulmonary vascular resistance (Wood units)	3.9 ± 1.7*	1.8 ± 0.7	2.0 ± 0.5
Pulmonary artery saturation (%)	54 ± 7*	71 ± 4	68 ± 4
Systemic artery saturation (%)	93 ± 4	97 ± 3	95 ± 2
IVUS vessel diameter (mm)	4.6 ± 0.8	3.8 ± 0.5	4.1 ± 0.9
Baseline pulmonary artery flow (ml/min)	16.8 ± 11.3	15.3 ± 11.0	17.1 ± 12.2

*$p < 0.05$ (analysis of variance [ANOVA]). Values presented are mean value ± SD or number. FEV1 = forced expiratory volume at 1 s; Group I = chronic heart failure with secondary pulmonary hypertension; Group II = chronic heart failure with normal pulmonary artery pressure; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; PCW = pulmonary capillary wedge pressure; TLC = total lung capacity.

8F sheath in 10 of 12 Group I patients, 8 of 10 Group II patients and 6 of 8 control patients to determine an in vivo dose-response curve. Continuous real-time intravascular ultrasound images of pulmonary artery area throughout the cardiac cycle just distal to the sheath were recorded on 1/2-in. (1.3 cm) videotape. Systemic and pulmonary artery pressures were monitored during each infusion. After these three doses, the infusion was terminated, and baseline pulmonary artery area was reestablished. This was followed by a 3×10^{-5} mol/liter methylene blue infusion through the sheath alone and then in combination with 10^{-6} mol/liter of acetylcholine. Methylene blue was used to determine the effect of inhibition of endothelium-dependent relaxing factor synthesis on vascular responses to the lowest dose of acetylcholine (6). In 17 patients (6 each from Groups I and II and 5 from the control group), a 5-μg/ml infusion of indomethacin was added to the acetylcholine/methylene blue infusion. Indomethacin was utilized to evaluate what effect thromboxane and prostacyclin synthesis had on the acetylcholine responses observed after inhibition of endothelium-dependent relaxation. Nitroglycerin (50 to 100 μg/min) was infused in 14 patients in Groups I and II and 6 control subjects to assess endothelium-independent relaxation.

Statistical analysis. Pulmonary artery area measurements for each infusion were the average of three to four consecutive cardiac cycles. Each area measurement was obtained from an off-line reading station and represented the average of the smallest and largest areas throughout the cardiac cycle. Responses to each infusion were compared using analysis of variance (ANOVA) (Student-Newman-Keuls multiple comparison procedure). A p value < 0.05 was considered significant.

Results

Patient characteristics. Table 1 lists the baseline clinical and hemodynamic findings in the three groups at the time of study. The etiology of the cardiomyopathy was ischemic in 14 patients with heart failure: 7 in Group I and 7 in Group II. The duration of heart failure symptoms was not different between Groups I and II. Pulmonary function tests were performed in six Group I and seven Group II patients. There were no differences between Groups I and II in forced expiratory volumes or total lung capacities. However, in the patients with secondary pulmonary hypertension (Group I), pulmonary artery oxygen saturation was significantly lower, and baseline pulmonary vascular resistance was higher. Baseline pulmonary artery flow in the vessel segment studied was not different among the three groups.

Pulmonary artery morphology by intravascular ultrasound. Pulmonary artery plaque was identified in 11 (50%) of 22 arteries in the patients with chronic heart failure. Five (45%) of the 11 arteries with plaque were in patients with pulmonary hypertension, whereas 6 (55%) were in patients with normal pulmonary artery pressure. The plaque was eccentric in 10 of the 11 patients. It was brightly echogenic in

Table 2. Percent Change in Pulmonary Artery Area in Response to Acetylcholine Before and After Administration of Methylene Blue

	Percent Change From Baseline		
	ACH Alone	MB Alone	MB/ACH
Group I	0.5 ± 3.4%	0.6 ± 3.7%	−0.1 ± 4.3%
Group II	1.1 ± 4.5%	−0.3 ± 5.5%	−10.4 ± 7.8%*
Control group	2.3 ± 9.9%	−0.8 ± 5.6%	−1.7 ± 3.9%

*$p < 0.05$ (ANOVA). Values presented are mean value ± SD. ACH = acetylcholine; MB = methylene blue; other abbreviations as in Table 1.

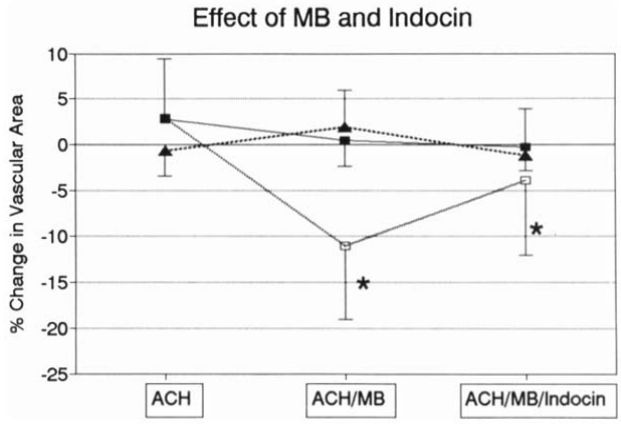

Figure 3. Graphic demonstration of the marked vasoconstriction in patients with chronic heart failure and normal pulmonary artery pressure (open squares) to low dose acetylcholine (ACH) after pretreatment with methylene blue (MB). After indomethacin (Indocin), there was a significant reversal of the pulmonary artery constriction in the patients with chronic heart failure who maintained normal pulmonary artery pressure. **Solid triangles** = patients with chronic heart failure and secondary pulmonary hypertension; **solid squares** = control patients. *$p < 0.05$ compared with control and chronic heart failure with secondary pulmonary hypertension (analysis of variance).

all cases but did not cause shadowing. In contrast to patients with heart failure, only two (25%) of the eight control patients had evidence of plaque.

Responses to acetylcholine. Figure 1 illustrates the changes in pulmonary arterial area to incremental doses of acetylcholine. Although none of the three groups exhibited significant changes in arterial area to 10^{-6} or 10^{-5} mol/liter of acetylcholine, there was a significant decrease in pulmonary arterial area in Group II patients (chronic heart failure with normal pulmonary artery pressure) in response to 10^{-4} mol/liter of acetylcholine (11.5 ± 11.9% decrease vs. 5.2 ± 10.0% decrease in control subjects and 0.8 ± 4.0% increase in Group I patients, $p < 0.05$, ANOVA). Among the six control patients who received incremental infusions of acetylcholine, vasoconstriction was elicited in three, and the other three had no significant area change in response to the 10^{-4} mol/liter infusion.

Responses to acetylcholine after methylene blue. Table 2 lists the percent pulmonary artery area responses to methylene blue alone and to 10^{-6} mol/liter of acetylcholine after pretreatment with methylene blue. In contrast to 10^{-6} mol/liter of acetylcholine alone, there was now significant vasoconstriction in the Group II patients (heart failure and normal pulmonary artery pressure) (10.4 ± 7.8% area decrease in Group II vs. 0.1 ± 4.3% decrease in Group I and 1.7 ± 3.9% decrease in control patients, $p < 0.05$, ANOVA). There was no significant change in pulmonary vascular area in any of the three groups in response to methylene blue alone (Table 2).

Figure 2 is a representative intravascular ultrasound image of a pulmonary artery in a Group II patient with chronic heart failure and normal pulmonary artery pressure that illustrates the vasoconstriction that occurred in response to acetylcholine *only* after pretreatment with methylene blue.

Responses to indomethacin after acetylcholine/methylene blue infusion. Figure 3 graphically illustrates the change in pulmonary vascular area in response to acetylcholine, acetylcholine after pretreatment with methylene blue and after a

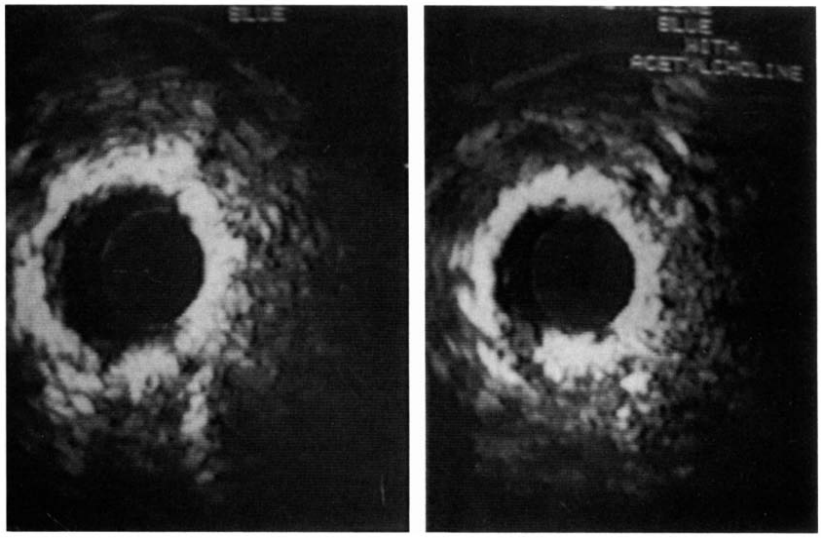

Figure 2. Intravascular ultrasound images of the pulmonary artery in a patient with chronic heart failure and normal pulmonary artery pressure. **Left,** Response to methylene blue alone. **Right,** Response to 10^{-6} mol/liter of acetylcholine after pretreatment with methylene blue. Note the marked constriction of the pulmonary artery after endothelium-derived relaxing factor synthesis is inhibited.

5-μg/ml infusion of indomethacin was added to the 10^{-6} mol/liter acetylcholine/methylene blue infusion. There was complete reversal of the pulmonary artery constriction seen with acetylcholine/methylene blue in four of six Group II patients. The mean increase in vessel area after indomethacin in Group II was significantly different from the responses seen in the other groups (8.0 ± 7.6% increase in area in Group II vs. 3.0 ± 3.4% constriction in Group I and 0.6 ± 3.9% constriction in the control group; $p < 0.05$, ANOVA). Of three control patients taking aspirin, two had constriction and one had dilation in response to indomethacin, whereas two not taking aspirin either had no change in vessel area or had constriction. There were no significant changes in local pulmonary artery pressures (measured from the sheath) in response to any of the infusions.

Endothelium-independent pulmonary artery responses. In 14 patients with chronic heart failure (8 with pulmonary hypertension and 6 with normal pulmonary artery pressure) and 6 control patients, pulmonary artery responses to nitroglycerin were also evaluated. In the patients with chronic heart failure, five of six with normal pulmonary artery pressure and six of eight with pulmonary hypertension had dilation in response to nitroglycerin, indicating the absence of differential responses to endothelium-independent vasodilators in heart failure with or without pulmonary hypertension. In contrast, only three of the six control patients had dilation after nitroglycerin.

Discussion

This study demonstrates that in the pulmonary artery of humans with chronic heart failure, the response to a local infusion of acetylcholine depends to a large extent on whether pulmonary artery pressures remain normal. Patients with chronic heart failure who maintain normal pulmonary artery pressure exhibit significant vasoconstriction in response to acetylcholine when endothelium-dependent vasodilator responses are blocked by methylene blue. These findings are consistent with the hypothesis that the pulmonary vascular endothelium may play a significant role in preventing vasoconstriction in chronic heart failure.

We used local infusions of methylene blue to inhibit pulmonary vasodilator responses to acetylcholine because of its extensive use in the pulmonary circulation for this purpose. Hyman et al. (6) demonstrated in the feline pulmonary circulation that methylene blue selectively inhibits endothelium-dependent vasodilatory responses. Methylene blue has also been shown to stimulate superoxide anions (8). However, its main effects in the pulmonary circulation, appear to be inhibition of guanylate cyclase (7,9,10) because it also inhibits pulmonary artery vasodilator responses to nitroglycerin and bradykinin (10).

In this study, vasoconstriction in response to acetylcholine in the patients with chronic heart failure with normal pulmonary artery pressure occurred in two settings. First, it was seen when acetylcholine was given in the highest concentration (10^{-4} mol/liter). Second, it was seen in response to lower concentrations of acetylcholine (10^{-6} mol/liter) after pretreatment of the pulmonary vessel segment with methylene blue. These results suggest that acetylcholine was inducing endothelium-mediated vasodilation that inhibited simultaneous acetylcholine-mediated constriction.

Endothelium-dependent inhibition of pulmonary vasoconstriction. Although we observed no difference in response to the lowest concentration of acetylcholine alone in any of the three groups, pretreatment of the same vessel with methylene blue resulted in significant vasoconstriction in the patients with chronic heart failure who maintained normal pulmonary artery pressure. This indicates that endothelium-dependent vasodilatory responses to acetylcholine may be responsible for inhibiting vasoconstriction to acetylcholine in this group. The endothelium in these patients demonstrates a greater inhibitory role even when compared with that in the control patients, who had normal left ventricular systolic function and pulmonary artery pressures. In contrast, the patients with chronic heart failure who developed pulmonary hypertension did not have vasoconstriction in response to either the 10^{-6} mol/liter infusion after methylene blue or to higher concentrations of acetylcholine. Therefore, acetylcholine does not appear to stimulate endothelium-dependent vasodilation or even vasoconstriction in the presence of secondary pulmonary hypertension.

Pulmonary artery constriction in response to acetylcholine. The vasoconstriction that we observed in response to the highest dose of acetylcholine (10^{-4} mol/liter) in the patients with chronic heart failure and normal pulmonary artery pressure was not seen in the patients with secondary pulmonary hypertension or in the control group. The are two possible reasons for these differences. First, lower rest tone in the patients with heart failure who maintained normal pulmonary artery pressure may have influenced the response to acetylcholine. Hyman and Kadowitz (11) demonstrated in the feline pulmonary vascular bed that acetylcholine increased lobar artery pressure only when rest tone was low. Barman et al. (12) observed that higher concentrations of acetylcholine increased vascular resistance in the pulmonary artery under rest conditions. These investigators found that the vasoconstrictor responses were attenuated or reversed when rest vascular tone was increased. This may explain why the patients with chronic heart failure with secondary pulmonary hypertension in our study had no constriction in response to even the highest concentrations of acetylcholine.

Second, acetylcholine may induce enhanced thromboxane synthesis in patients with chronic heart failure and normal pulmonary artery pressure. In four of the six patients with heart failure and normal pulmonary artery pressure, the addition of an indomethacin infusion caused complete reversal of the constriction seen in response to the acetylcholine/methylene blue infusion. These observations are consistent with those seen in the pulmonary artery of animal models as well. Altiere et al. (13) demonstrated that thromboxane A_2

mediates acetylcholine-induced vasoconstriction in the pulmonary artery of rabbits. Removal of the pulmonary vascular endothelium in the rabbits significantly decreased the vasoconstriction, suggesting that *both* vasodilator and vasoconstrictor responses to acetylcholine in the pulmonary circulation may be endothelium dependent.

High rest thromboxane production has been observed in humans with secondary pulmonary hypertension (14). This high level of thromboxane may also be an important mediator of pulmonary artery vasoconstriction in chronic heart failure. In our study, however, thromboxane-mediated vasoconstriction was seen only in the patients with heart failure with normal pulmonary artery pressure and only after inhibition of endothelium-derived relaxing factor with methylene blue.

Limitations of the study. The observation that acetylcholine did not cause direct vasodilation and did not cause vasoconstriction after endothelium-dependent relaxing factor synthesis was inhibited in the patients with heart failure and pulmonary hypertension suggests defective endothelial function. However, it does not reveal which process occurred first (pulmonary hypertension or abnormal endothelium-dependent responses). It is possible that the development of secondary pulmonary hypertension led to defective endothelial function. Alterations in endothelial cell function have occurred in response to isolated increases in pressure (15). Although pulmonary artery pressure appears to play a role in predicting the response to acetylcholine, the augmented pulmonary artery constrictor responses to acetylcholine in the patients with heart failure who maintain normal pulmonary artery pressure compared with responses in our control patients suggest a primary role of the pulmonary vascular endothelium in modulating tone.

Other factors, such as local pulmonary artery flow rates and hypoxia, may have influenced the responses we observed (Table 1). Pulmonary artery oxygen saturation, which may affect endothelial response, was lower in the patients with secondary pulmonary hypertension. The baseline flow in the vessel segments studied was not different between the two heart failure groups. Because we did not assess flow changes in response to acetylcholine, however, we do not know whether the different responses that we observed between the heart failure groups also occur at the microvascular level.

We did not see vasoconstriction in response to the infusion of methylene blue alone in any of the groups (Table 2). This would be expected in the patients with chronic heart failure who maintained normal pulmonary artery pressure if basal levels of endothelium-derived relaxing factor were increased. It may be that a higher concentration or a longer duration of methylene blue infusion than the one used in this study are required to demonstrate this. Kadowitz et al. (16) reported that pulmonary artery constriction in response to methylene blue is a dose-dependent phenomenon, and Fineman et al. (17) showed that pulmonary artery vasoconstriction in response to methylene blue is time-dependent.

Although these findings suggest intact endothelial responses in patients with chronic heart failure who maintain normal pulmonary artery pressure, we did not observe a significant vasodilator response to acetylcholine alone either in these patients or in the control group. This may be due to several factors. The control group was slightly older (Table 2) and also had significant atherosclerotic vascular disease. Both of these factors may cause defective endothelial responses. Second, acetylcholine responses in the pulmonary artery appear to be tone-dependent (11). Only three of six control patients had dilation in response to nitroglycerin, a finding that suggests that resting vascular tone may have been different within the control group. Finally, because vasoconstrictor responses to acetylcholine also appear to be dose-dependent (16), a lower concentration of acetylcholine (10^{-8} or 10^{-7} mol/liter) may have elicited significant vasodilation in the patients with chronic heart failure with normal pulmonary artery pressure and in the control group.

Conclusions. Despite these limitations, our findings support the hypothesis that the pulmonary vascular endothelium may play a significant role in attenuating vasoconstriction in the pulmonary artery in chronic treated heart failure. Further study of the human pulmonary artery in chronic heart failure is indicated to define whether intact functional endothelium prevents secondary pulmonary hypertension from occurring. Specifically, the physiologic role of basal levels of endothelium-derived relaxing factor in preventing pulmonary artery constriction in human heart failure needs to be defined. Using intravascular ultrasound and the infusion protocol of this study, the basal activity and inhibitory role of the endothelium can be further delineated in human heart failure by infusing either specific inhibitors of endothelium-dependent relaxing factor synthesis or known vasoconstrictors that are normally inhibited by the endothelium.

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